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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/473,872	12/28/1999	KYONGGEUN YOON	JEFF-Y0001	1565

7590 12/06/2001

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EXAMINER

WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 12/06/2001

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/473,872

Applicant(s)

YOON, KYONGGEUN

Examiner

Joseph T. Weitach

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 13.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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Continued Prosecution Application

The request filed on September 21, 2001, paper number 15, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/473,872 is acceptable and a CPA has been established. An action on the CPA follows.

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

This application is an original application filed December 28, 1999.

Applicants amendment filed September 21, 2001, paper number 16, has been received and entered. Claims 1-4, 8-10, 19, 23-25 and 33 have been amended. Claims 1-40 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-4, 19, 32, and 33 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

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to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

Claims 1-40 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for creating stable genetic modifications in the skin of mice comprising genetic and phenotypic alteration in mouse tyrosinase, COL7A1, and KRT17 genes *using specific RDOs disclosed in the instant disclosure*, does not reasonably provide enablement for methods for making and using stable genetic modifications in the skin of humans and other animals comprising genetic and phenotypic alterations involving the broad scope of genes recited in the claims is withdrawn.

Applicant argues that the sequences encompassed by the instantly claimed invention were known at the time of filing, providing a listing of Genbank numbers of the human genes specifically recited (see Exhibit 1). Further, given the guidance of the instant specification and the level of skill in the art, the artisan would understand how to design chimeric RDOs in order to carry out the claimed methods. Applicant argues that there is no requirement to describe every detail of an invention, citing *In re Hayes* for support of there arguments. See Applicant's amendment, pages 8-9. In addition, Applicant argues that while references speculate that the instantly claimed method may not be reproducible, the preponderance of pre- and post-filing art demonstrating the successful use of RDOs demonstrates a fair predictability to the instantly claimed methods. Further, Applicant points out that Strauss, whose Nature Medicine (1998) reference was used to establish the unpredictability in the art, has published a report, NAR

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(1999), establishing the usefulness of the instantly claimed method for studying chimera-directed gene repair which uses RDOs. See Applicant's amendment, pages 10-14.

Applicant's arguments have been found persuasive. In view of the public availability of the specific nucleic acid sequences recited in the instant claims, and the pre- and post-filing art of record demonstrating that RDOs to various genes have been successfully made and used for the introduction of genetic alteration to genes in the skin and other tissues, Examiner agrees that the teachings in the instant specification provides adequate guidance for and support that Applicants were in possession of methods for the generation and use of an RDO. Though the art suggests that optimization of RDOs may be necessary for a given gene/mutation, given the guidance in the instant specification and the availability of a gene sequence, Examiner agrees that one of skill in the art could affect a stable modification of a selected gene in the cells of the skin, wherein the gene modification results in phenotypic change in the skin.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

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Claim 1 is unclear and confusing. The claim has been amended to recite 'bring about a stable genetic and phenotypic modification in the selected gene', however a phenotypic change does not occur in a gene, rather it results in a phenotypic change in the cell/tissue which has been affected. Amending the claim to reflect language used in claim 18 would obviate the basis of the rejection. Dependent claims 2-17 are included in this rejection because they fail to clarify the basis of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32-34 and 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexeev *et al.* (IDS reference).

Claims 32 broadly encompasses an animal model having a skin disorder wherein the disorder comprises a mutation generated in a gene which leads to said disorder. Claims 33-39 are drawn to specific genes and specific types of mutations. First, it is noted that the animal model is presented as a product by process claim. Where the claimed and prior art products are identical or substantially identical in structure or composition, a *prima facie* case of either

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anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01. In the instant case, Alexeev *et al.* teach an animal whose skin cells display the phenotype of albino melanocytes. Though the mutation is not introduced by administration of an RDO, the animal with a mutation in the Tyr gene represents an animal model having a skin disorder resulting from a genetic alteration. Therefore, the animals taught by Alexeev *et al.* represent an animal model for the study of a mutation in the Tyr gene, and thus, anticipate the claims.

Claims 32-33, 35 and 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Christiano *et al.* (PNAS, 91:3549-3553, 1994).

The instant claims are drawn to an animal generated by introducing a mutation into a gene by use of an RDO. As noted above, "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of

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showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See also *In re Best*, 562 F.2d at 1255, 195 USPQ at 433., *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01. Christiano *et al.* teach a pedigree of Finnish individuals whose genome contains a mutation in the COL7A1 gene, which results in Epidermolysis bullosa and the phenotype of blistering skin. Therefore, the animals taught by Christiano *et al.* represent an animal model for the study of a mutation in the COL7A1 gene, and thus anticipate the claims.

Claims 32-33 and 36-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Uttam *et al.* (PNAS 93:9079-9084, 1996).

The instant claims are drawn to an animal model generated by introducing a mutation into a gene by use of an RDO. As noted above, “When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). In the instant case, Uttam *et al.* teach a pedigree of German individuals whose genome contains a mutation in the keratin 14 gene, resulting in Epidermolysis bullosa with the phenotype of mottled pigmentation. Therefore, the animals taught by Uttam *et al.* represent an animal model for the study of a KRT17 gene, and thus anticipate the claims.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon *et al.* (PNAS, 1996) and Alexeev *et al.* (Nature Biotech, 1998) in further view of, Uttam *et al.* (PNAS, 1996), Christiano *et al.* (PNAS, 1994) and Cole-Strauss *et al.* (IDS reference; Science, 1996).

Claims 1-31 and 40 are drawn to methods of introducing a stable genetic change into the genome of a skin cell of an animal. Dependent claims recite specific genes known in the art as potential target sequences, and various types of mutations which could be introduced to either generate a mutation or correct an existing mutation. The means of introducing the genetic alteration is through the administration of chimeric RNA-DNA oligonucleotide termed RDO. The use of RDOs to generate genetic alterations in the genome of mammalian cells has been demonstrated previously in the art. Yoon *et al.* teach that an RDO can be used to generate a stable genetic alteration in cells in culture and state that the strategy can be extended to other genes and gene targeting approaches (summarized in abstract). Alexeev *et al.* demonstrate that an RDO can be used to create a stable change in the tyrosinase gene in an animal (entire reference). A mutation in the tyrosinase gene results in ablation of tyrosinase activity and the phenotype of albino melanocytes. Cole-Strauss *et al.* demonstrate and provide evidence that

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RDOs can be used to successfully target alterations in other genes in human cells. In total, the combined teachings of Yoon *et al.*, Alexeev *et al.* and Cole-Strauss *et al.* provide the guidance and demonstrate the ability to generate an RDO to a gene of interest, wherein administration of the RDO to the animal results in a stable genetic alteration in the genome of a cell. Moreover, Alexeev *et al.* demonstrate that one can successfully target the tyrosinase gene which is responsible for a given phenotype in skin cells. Uttam *et al.* and Christiano *et al.* teach mutations in the human keratin14 gene and Col7A1 genes, respectively. Uttam *et al.* and Christiano *et al.* establish that genetic mutations in humans were known at the time of filing and that said mutations resulted in a phenotypic change in the skin cells. Given that RDOs were successfully used to introduce a genetic change in the cells of animals, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to use the methods specifically taught by Yoon *et al.*, Alexeev *et al.* and Cole-Strauss *et al.* to target other genes known in the art as exemplified by Uttam *et al.* and Christiano *et al.* Each Yoon *et al.*, Alexeev *et al.* and Cole-Strauss *et al.* provide the motivation to extend and use the specific RDO methodology to other genes of interest. Though Yoon *et al.*, Alexeev *et al.* and Cole-Strauss *et al.* suggest that the efficiency for use of RDOs in other cell types may require optimization, there would have been a reasonable expectation of success given the results presented in the references and the skill in the art at the time of the claimed invention to target the human genes taught by Uttam *et al.* and Christiano *et al.*, or any other gene known in the art to be the source of a genetic disease.

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Thus, the claimed invention, as a whole was *prima facie* obvious absent to the evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732.

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Deborah Crouch

Joseph T. Woitach

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